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# Catalytic cyclopropanation of methylenecyclobutanes using ethyl nitrodiazoacetate. Synthesis of spirohexane amino acids

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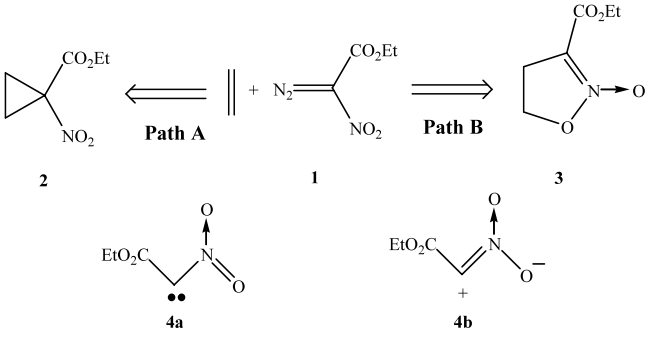
**Abstract**—The reaction of ethyl nitrodiazoacetate with a series of methylenecyclobutanes was studied and both [1+2]- and [2+3]-cycloaddition pathways were observed depending on olefin structure. Amino acids of a spirohexane type were synthesized from methylenecyclobutanes by a three-step synthesis.


As a part of our continuing studies devoted to the triangulanes and their derivatives[1] as well as to the ligands of glutamate receptors[2] we have now carried out research on the synthesis of novel polycyclic amino acids, containing a cyclopropane framework. In fact, cyclopropane analogues of physiologically active compounds can be considered as conformationally restricted analogues, with potentially interesting biological activities (examples for ligands of glutamate receptors, see[2a,3]).

The development of an efficient and expedient method for the synthesis of cyclopropane amino acids via reduction of a nitro group is of particular interest.




Transition metal-catalyzed cyclopropanation of alkenes with nitro diazoesters[4] (**Path A**) seemed to be a direct approach for preparation of 1-nitrocyclopropanecarboxylates of type **2**. Starting ethyl nitrodiazoacetic ester (**1**, ENDA) is readily available and can be easily prepared by a diazotransfer reaction of ethyl diazoacetate with triflyl azide.[5] In general, 1-nitrocylopropanecarboxylates (**Path A**) can be considered an amino acid equivalent after reduction of the nitro group.

However, there is one obvious possible complication: analysis of the resonance structures of transient nitrocarboethoxycarbene **4** indicates that it can be considered as a 1,3-dipole **4b** and, hence, could participate in [2+3]-cycloaddition (**Path B**) to give an isoxazoline structure. To the best of our knowledge, this pathway has not been observed in cycloaddition reactions of **1**; however, the thermal rearrangement of nitrocyclopropanes **2** into isoxazolines **3** is known.[4] In fact, this type of [1,3]-sigmatropic rearrangement[6] of cyclopropane systems connected to a double bond, is well documented.[7]

In the present study, we have examined (i) this synthetic approach for the preparation of some unnatural amino acids containing a spirohexane moiety and (ii) the structural dependence of **Path A** versus **Path B** for some cyclopropane/cyclobutane containing olefins.

First, we studied the cycloaddition reactions of ENDA **1**, with olefins **5a–c** of the methylenecyclobutane series (Table 1).

*Keywords*: ethyl nitrodiazoacetate; spirohexane amino acids; [1+2]-cycloaddition; [2+3]-cycloaddition; 1-ethoxycarbonyl-nitropolyspirocycloalkanes.
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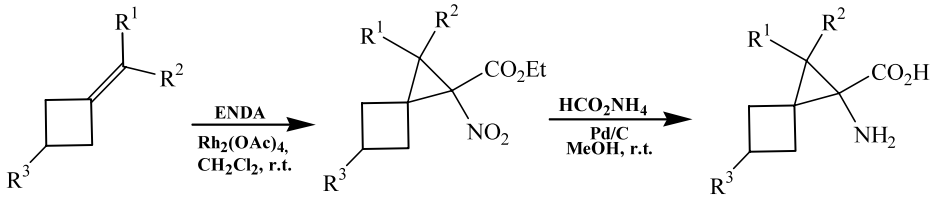
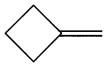
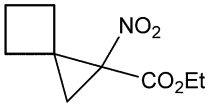
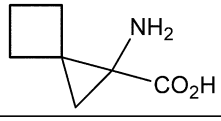
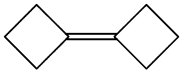
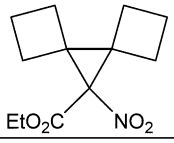
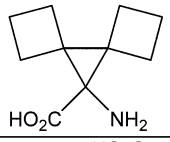
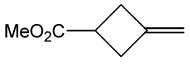
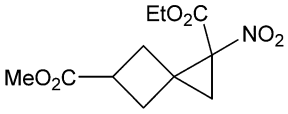
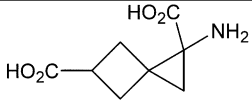



**5a-c** **6a-c** **7a-c**

**a** $R^1=R^2=R^3=H$; **b** $R^1,R^2 = -CH_2CH_2CH_2-$, $R^3 =H$ ; **c** $R^1=R^2=H$, $R^3 = COOCH_3$

**Table 1.**

| Entry | Alkene | Entry | Nitro ester | Yield, % | Entry | Amino acid | Yield, % |
|---|---|---|---|---|---|---|---|
| **5a** |  | **6a** |  | 89 | **7a** |  | 56 |
| **5b** |  | **6b** |  | 59 | **7b** |  | 62 |
| **5c** |  | **6c** |  | 78 | **7c** |  | 53 |

The reaction of ENDA with methylenecyclobutanes **5** in the presence of catalytic amounts of dirhodium tetraacetate afforded ethyl nitrospiro[2.3]hexanecarboxylates **6** in good yields (Table 1) in accordance with **Path A** ([1+2]-cycloaddition).[8] We note first, that bicyclobutylidene **5b** gives the corresponding tricyclic adduct **6b** as a single product (Table 1) and, hence, even the tetrasubstituted C=C double bond in **5b** possesses sufficient reactivity for addition of the transient nitrocarbethoxycarbenoid. Second, the presence of the electron-withdrawing ester group at C-3 of the cyclobutane ring of alkene **5c** does not significantly influence the product yield, nitroester **6c** being obtained in high yield (Table 1) as a mixture of two diastereomers in a ratio of 1.6:1 (according to NMR data).

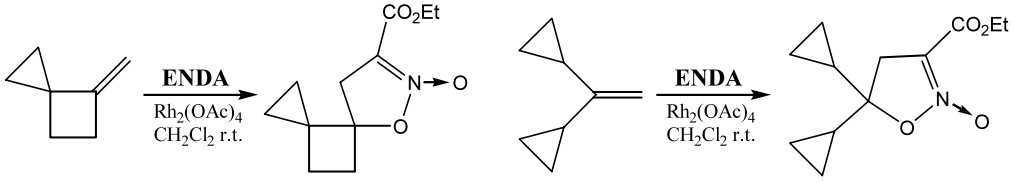
However, the reaction of methylenespirohexane **8** with ENDA gave a completely different result. Instead of the expected [1+2]-cycloadduct of type **2**, we obtained the tricyclic isoxazoline-*N*-oxide **9** in a moderate yield under the same reaction conditions[8] and, hence, the reaction proceeds via **Path B** ([2+3]-cycloaddition).

The compound **8** can also be considered as a vinyl cyclopropane, and following literature precedents,[6,7] it is possible to speculate that exactly this fragment is responsible for the observed result.

To test this hypothesis we exposed 1,1-dicyclopropylethylene **10** to this reaction. Indeed, in accordance with expectation, the reaction of **10** with ENDA gave the isoxazoline *N*-oxide.[8] Of course, more information is needed to prove this hypothesis, but it certainly may be considered as a guideline for future studies.

In the second part of this work, we have developed a protocol for the synthesis of some cyclopropane amino acids **7** from the nitrocyclopropanecarboxylates **6** obtained. The method involves two steps, namely reduction followed by hydrolysis.

The crucial factor in the reduction of the cyclopropane nitro esters **6** is the choice of an effective reducing agent and a catalyst. We have tested some known catalytic systems, namely $NaBH_4$–Pd/C,[9] Raney Ni–$N_2H_4\times$




**8** **9** (55%) **10** **11** (52%)

$HCO_2H$[10] and $HCO_2NH_4$–Pd/C[11]. The most suitable proved to be ammonium formate in the presence of catalytic amounts of palladium on charcoal.[11] Reduction with this system took place quantitatively forming the corresponding amino esters with no by-products.[12,13] Hydrolysis then smoothly led to the corresponding amino acids **7**, but the separation of the product from inorganic compounds reduced yields to 50–60%.

The amino acids **7** obtained with this method are shown in Table 1. It should be noted that amino acid **7c** containing a second carboxyl group is a conformationally restricted analogue of glutamic acid and this compound should be considered as a potential ligand of methabotropic glutamate receptors.

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8. *General procedure for the preparation of compounds* **6**, **9**, **11**: Ethyl nitrodiazoacetate **1** (1 mmol) was added slowly to a stirred mixture of alkene (5–10 mmol) and $Rh_2(OAc)_4$ (3% mol) at 0–5°C. Then the reaction mixture was stirred at ~20°C for 1 h. Excess alkene was removed under reduced pressure, the catalyst was filtered through silica gel and the product (a colorless oil) was isolated by flash column chromatography (ether-light petroleum ether as the eluent, 0–30%).

**1-Nitro-spiro[2.3]hexane-1-carboxylic acid ethyl ester 6a**: $R_f$ 0.45 ($SiO_2$, hexane–ether 3:1) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.24 (m, $^3J=7.2$ Hz, 2H, $OCH_2$), 2.60–2.40 (m, 2H, cy-Bu), 2.35–2.20 (m, 2H, cy-Bu), 2.15–1.90 (m, 2H, cy-Bu), 2.14 (AB-system, $^2J=6.8$ Hz, 1H, $CH_2$, cy-Pr), 1.83 (AB-system, $^2J=6.8$ Hz, 1H, $CH_2$, cy-Pr), 1.27 (t, $^3J=7.2$ Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.25 (C̲OOEt), 72.07 (C), 62.28 ($^1J_{C,H}=151$ Hz, $OCH_2$), 38.18 ($C_{spiro}$), 28.19 ($^1J_{C,H}=138$ Hz, $CH_2$, cy-Bu), 27.66 ($^1J_{C,H}=139$ Hz, $CH_2$, cy-Bu), 24.87 ($^1J_{C,H}=168$ Hz, $CH_2$, cy-Pr), 15.37 ($^1J_{C,H}=139$ Hz, $CH_2$, cy-Bu), 13.90 ($^1J_{C,H}=127$ Hz, $CH_3$). Anal. calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.34; H, 6.67; N, 7.11.

**9-Nitro-dispiro[3.0.3.1]nonane-9-carboxylic acid ethyl ester 6b**: $R_f$ 0.65 ($SiO_2$, hexane–ether 3:1) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.23 (m, $^3J=7.2$ Hz, 2H, $OCH_2$), 2.40–2.25 (m, 4H, cy-Bu), 2.20–1.95 (m, 8H, cy-Bu), 1.27 (t, $^3J=7.2$ Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.42 (C̲OOEt), 74.76 (C), 62.12 ($OCH_2$), 42.72 ($C_{spiro}$), 24.65 (2×$CH_2$, cy-Bu), 24.42 (2×$CH_2$, cy-Bu), 15.62 (2×$CH_2$, cy-Bu), 14.26 ($CH_3$). Anal. calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.41; H, 7.19; N, 5.98.

**1-Nitro-spiro[2.3]hexane-1,5-dicarboxylic acid 1-ethyl ester 5-methyl ester 6c**: a mixture of two isomers (**A**/**B**=8:5); $R_f$ 0.50 ($SiO_2$, hexane–ether 3:1) $^1$H NMR (300 MHz, $CDCl_3$) for the mixture of two isomers: $\delta$ 3.98 (m, 2H+2H, $OCH_2$), 3.41 (s, 3H, $CH_3$, for isomer **A**), 3.37 (s, 3H, $CH_3$, for isomer **B**), 3.10–2.85 (m, 1H +1H, cy-Bu), 2.60–2.45 (m, 1H+1H, cy-Bu), 2.35–2.00 (m, 3H+3H, cy–Bu), 1.91 (AB-system, $^2J=6.8$ Hz, 1H, $CH_2$, cy-Pr, for isomer **B**), 1.85 (AB-system, $^2J=7.1$ Hz, 1H, $CH_2$, cy-Pr, for isomer **A**), 1.65 (AB-system, $^2J=6.8$ Hz, 1H, $CH_2$, cy-Pr, for isomer **B**), 1.59 (AB-system, $^2J=7.1$ Hz, 1H, $CH_2$, cy-Pr, for isomer **A**), 0.99 (t, $^3J=7.1$, 3H+3H, $OCH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) for isomer **A**: $\delta$ 174.05 (C̲OOMe), 163.41 (C̲OOEt), 71.53 (C), 61.97 ($OCH_2$), 51.22 ($OCH_3$), 34.71 ($C_{spiro}$), 31.73 (CH), 30.57 ($CH_2$, cy-Bu), 30.01 ($CH_2$, cy-Bu), 26.97 ($CH_2$, cy-Pr), 13.30 ($CH_3$). $^{13}$C NMR (75 MHz, $D_2O$) for isomer **B**: $\delta$ 173.38 (COOMe), 163.31 (COOEt), 70.76 (C), 61.97 ($OCH_2$), 51.16 ($OCH_3$), 33.79 ($C_{spiro}$), 31.23 (CH), 30.87 ($CH_2$, cy-Bu), 29.94 ($CH_2$, cy-Bu), 27.05 ($CH_2$, cy-Pr), 13.30 ($CH_3$). Anal. calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.45. Found: C, 51.33; H, 5.90; N, 5.46.

**6-Oxy-5-oxa-6-aza-dispiro[2.0.4.2]dec-6-ene-7-carboxylic acid ethyl ester 9**: $R_f$ 0.35 ($SiO_2$, hexane–ether 3:1) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.27 (q, $^3J=7.2$ Hz, 2H, $OCH_2$), 3.38 (s, 2H, $CH_2$), 2.75–2.60 (m, 1H, cy-Bu), 2.40–2.28 (m, 1H, cy-Bu), 2.10–1.86 (m, 2H, cy-Bu), 1.30 (t, $^3J=7.2$ Hz, 3H, $CH_3$), 1.11–1.02 (m, 1H, cy-Pr), 0.67–0.50 (m, 3H, cy-Pr). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.21 (C̲OOEt), 109.04 (C), 84.17 (C-O), 61.79 ($^1J_{C,H}=147$ Hz, $OCH_2$), 39.83 ($^1J_{C,H}=139$ Hz, C̲$H_2$C=), 34.27 ($^1J_{C,H}=137$ Hz, $CH_2$, cy-Bu), 29.82 ($C_{spiro}$), 22.55 ($^1J_{C,H}=140$ Hz, $CH_2$, cy-Bu), 14.10 ($^1J_{C,H}=127$ Hz, $CH_3$), 10.43 ($^1J_{C,H}=163$ Hz, $CH_2$, cy-Pr), 8.95 ($^1J_{C,H}=161$ Hz, $CH_2$, cy-Pr). Anal. calcd for $C_{11}H_{15}NO_4$: C, 58.86; H, 6.70; N, 6.31. Found: C, 58.66; H, 6.71; N, 6.22.

**5,5-Dicyclopropyl-2-oxy-4,5-dihydro-isoxazole-3-carboxylic acid ethyl ester 11**: $R_f$ 0.30 ($SiO_2$, hexane–ether 3:1) $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.01 (q, $^3J=7.1$ Hz, 2H, $OCH_2$), 3.06 (s, 2H, $CH_2$), 1.24 (t, $^3J=7.1$ Hz, 3H, $CH_3$), 1.10–1.01 (m, 2H, cy-Pr), 0.50–0.38 (m, 6H, cy-Pr). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 158.85 (C=OOEt), 109.07 (C), 82.30 (C-O), 61.48 ($OCH_2$), 39.35 ($CH_2C=$), 18.17 (2×CH, cy-Pr), 14.10 ($CH_3$), 1.11 (2×$CH_2$, cy-Pr), 0.15 (2×$CH_2$, cy-Pr). Anal. calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.18; H, 7.03; N, 5.57.

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12. The completeness of the reduction was confirmed by NMR spectroscopy and the amino esters were used for the next stage without isolation.
13. *General procedure for the preparation of amino acids* **7**: Ammonium formate (10 mmol) was added to a stirred mixture of ethyl 1-nitrocylopropanecarboxylate **6** (1 mmol), 10% Pd/C (10% mol) in anhydrous ethanol (10 ml). The reaction mixture was stirred for 40 h at rt, then the catalyst was removed by filtering. The solvent was evaporated under reduced pressure and the residue was stirred with 1N NaOH solution in ethanol (2 ml) for 48 h. The reaction mixture was acidified with 2N HCl to pH 3, the solvent was evaporated under reduced pressure, the residue was dissolved in the distilled water (2 ml), put on a Dowex 50 ion-exchange column and eluted with 0.9 N $NH_3$ solution, the solvent was evaporated and crystalline residue was recrystallized from ethanol–water (1:1).

**1-Amino-spiro[2.3]hexane-1-carboxylic acid 7a**: mp 281–282°C $^1$H NMR (300 MHz, $D_2O$) $\delta$ 2.75–2.50 (m, 2H, cy-Bu), 2.50–2.10 (m, 4H, cy-Bu), 1.92 (AB-system, $^2J=7.0$ Hz, 1H, $CH_2$, cy-Pr), 1.71 (AB-system, $^2J=7.0$ Hz, 1H, $CH_2$, cy-Pr). $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 171.95 (COOH), 40.28 (C), 33.50 ($C_{spiro}$), 27.08 ($^1J_{C,H}=136$ Hz, $CH_2$, cy-Bu), 25.70 ($^1J_{C,H}=138$ Hz, $CH_2$, cy-Bu), 24.87 ($^1J_{C,H}=164$ Hz, $CH_2$, cy-Pr), 15.49 ($^1J_{C,H}=141$ Hz, $CH_2$, cy-Bu). MS (EI, 70 eV): $m/z$ (%) = 113 $[M-C_2H_4]^+$ (16), 96 $[M-CO_2H]^+$ (100), 95 (20), 68 $[M-CO_2H-C_2H_4]^+$ (21), 67 (37), 41 (26), 39 (20).

**9-Amino-dispiro[3.0.3.1]nonane-9-carboxylic acid 7b**: mp 274–277°C $^1$H NMR (300 MHz, $D_2O$) $\delta$ 2.05–2.4 (m, 12H, cy-Bu). $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 170.48 (COOH), 43.58 (C), 38.80 ($C_{spiro}$), 23.83 (2×$CH_2$, cy-Bu), 22.24 (2×$CH_2$, cy-Bu), 14.94 (2×$CH_2$, cy-Bu). MS (EI, 70 eV): $m/z$ (%) = 153 $[M-C_2H_4]^+$ (37), 136 $[M-CO_2H]^+$ (60), 120 $[M-NH_2-CO_2H]^+$ (8), 108 $[M-CO_2H-C_2H_4]^+$ (100), 107 (58), 91 (19), 79 (33), 67 (16), 53 (21), 39 (21).

**1-Amino-spiro[2.3]hexane-1,5-dicarboxylic acid 7c**: (a mixture of two isomers (**A**/**B** = 7:5); mp 222–224°C $^1$H NMR (300 MHz, $D_2O$) for the mixture of two isomers: $\delta$ 3.78–3.41 (m, 1H+1H, cy-Bu), 2.95–2.62 (m, 4H+4H, cy-Bu), 2.09 (AB-system, $^2J=7.3$ Hz, 1H, $CH_2$, cy-Pr, for isomer **B**), 2.03 (AB-system, $^2J=7.4$ Hz, 1H, $CH_2$, cy-Pr, for isomer **A**), 1.93 (AB-system, $^2J=7.3$ Hz, 1H, $CH_2$, cy-Pr, for isomer **B**), 1.87 (AB-system, $^2J=7.4$ Hz, 1H, $CH_2$, cy-Pr, for isomer **A**). $^{13}$C NMR (75 MHz, $D_2O$) for isomer **A**: $\delta$ 178.97 (COOH), 171.44 (COOH), 40.26 (C), 32.73 (CH), 30.52 ($C_{spiro}$), 30.23 ($CH_2$, cy-Bu), 28.66 ($CH_2$, cy-Bu), 24.47 ($CH_2$, cy-Pr). $^{13}$C NMR (75 MHz, $D_2O$) for isomer **B**: $\delta$ 179.33 (COOH), 171.44 (COOH), 40.03 (C), 32.27 (CH), 30.95 ($C_{spiro}$), 30.04 ($CH_2$, cy-Bu), 29.14 ($CH_2$, cy-Bu), 24.61 ($CH_2$, cy-Pr). MS (EI, 70 eV): $m/z$ (%) = 140 $[M-CO_2H]^+$ (48), 139 (18), 113 $[M-CO_2H-CH_2-CH]^+$ (100), 95 $[M-CO_2H-CO_2H]^+$ (15), 94 (98), 93 (43), 68 (41), 67 $[M-CO_2H-CO_2H-C_2H_4]^+$ (100), 55 (31).